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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/645,706	08/24/2000	Keith V. Wood	341.005US1	3329

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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	

MAIL DATE	DELIVERY MODE
03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/645,706	Applicant(s) WOOD ET AL.	
	Examiner Rebecca E. Prouty	Art Unit 1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 February 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,3-6,9,11,12,15,18,20,21,24-39,41-45,47,60,67,69-71,74,76-78,80-88 and 90-96*.
   Claim(s) withdrawn from consideration: *64*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 3. Applicant's reply has overcome the following rejection(s): the claim objections and the 112, 2nd paragraph rejections of claims 18, 47, and 83 .

Claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 47, 60, 67, 69-71, 74, 76-78, 80-82, 85-88, and 90-96 remain rejected under 35 U.S.C. 112, second paragraph, as the recitation of "a reduced number of a combination of mammalian transcription factor binding sequences, intron splice sites, poly(A) addition sites and/or prokaryotic 5' noncoding regulatory sequences", "wherein the mammalian transcription factor binding sequences are present in a database of transcription factor binding sequences" and "known mammalian transcription factor binding sequences" is indefinite. Applicants argue that the terms "transcription factor binding sequences", "intron splice sites", "poly(A) addition sites" and "prokaryotic 5' noncoding regulatory sequences" are conventional in the art and argue that these terms are in fact used in the reference cited by the examiner in the 103 rejection. This is acknowledged. However, in the art these terms define a group of sequences related by function. The art does not define clearly **what** sequences are included in the group. Since applicants invention requires a skilled artisan to **quantify** the number of such sequences it is imperative that the artisan know explicitly what sequences are to be included and what sequences are not so one can in fact count them. In this regard, the examiner is requested to consider that Example 1 of the specification discloses that

synthetic click beetle luciferase sequences were prepared that had a reduced number of a combination of mammalian transcription factor binding sequences, intron splice sites, poly(A) addition sites and prokaryotic 5' noncoding regulatory sequences and as described in the declaration of Monika Wood, she determined the number of mammalian transcription factor binding sequences in the luc^{+} sequence of Sherf et al. (U.S. Patent No. 5,670,356), using software and a database that are available to the public and comparable to those disclosed in the application. However, it has never been the examiner's contention that given a clear set of sequences to be searched that calculation of the number was not possible, but that the claims are indefinite absent a clear definition of what sequences are encompassed by these terms. In both of the above examples, a specific list of sequences was used, but in the claims no such list is provided and thus the claims are indefinite as the scope will be different when different list of sequences are included. Applicants argue that although there may be new members added to the group of "mammalian transcription factors" over time, the independent claims in the present application provide that the synthetic nucleic acid molecules have a reduced number of a combination of mammalian transcription factor binding sequences, as a result of codon replacement of at least 25% of the codons

of a parent reporter nucleic acid sequence with mammalian high usage codons and mammalian codons that are not high usage. Thus, Applicant's synthetic polynucleotides are readily recognized by one of skill in the art. However, this is not persuasive as not all nucleic acids having at least 25% of the codons of a parent reporter nucleic acid sequence with mammalian high usage codons and mammalian codons that are not high usage are encompassed by the claims. The claims also require that the claimed polynucleotide have a **reduced number** of mammalian transcription factor binding sequences. It is this limitation that is indefinite as addition of new members to the group of mammalian transcription factor binding sequences can either increase the number of total mammalian transcription factor binding sequences in either one or both of the synthetic nucleic acid or the parent nucleic acid. Note if the new member were present one or more times only in the parent nucleic acid, a sequence that did not meet the limitation if searched without the new member might in fact meet the limitation when the new member was added and conversely if the new member were present one or more times only in the synthetic nucleic acid, a sequence that did meet the limitation if searched without the new member might in fact not meet the limitation when the new member was added

Applicants argue that the phrases "wherein the mammalian transcription factor binding sequences are those present in a database of transcription factor binding sequences" and "known mammalian transcription factor binding sequences" are definite, as one of skill in the art is aware of databases having transcription factor binding sequences. However, while a skilled artisan is aware of such databases, each database and in fact every version of each such database is different such that the phrases are unclear without the recitation of which such database and version thereof is intended.

The rejection of Claims 1, 3-6, 9, 11, 12, 15, 20-21, 24-33, 35-39, 41-45, 47, 60, 67, 69, 70, 81-82, 86-88, and 90-95 under 35 U.S.C. 112, first paragraph is maintained.

Applicants argue that with respect to reporter polypeptides, such as GFP, beetle luciferase, GUS, CAT, and beta-lactamase, applicant has provided evidence that it is well within the skill of the art to introduce substitutions into various reporter proteins and yield a variant protein with the activity of the corresponding wild-type reporter protein. However, it is noted that the evidence applicants refer to is available for specific GFPs, beetle luciferases, GUS or CAT enzymes, and beta-lactamases but each of these groups of reporter polypeptides includes vast numbers of proteins which

are not well characterized and often substantially different from those taught in the art. For example there are many different luminescent beetle species but only a few firefly and click beetle luciferases are well characterized in the art and even these enzymes differ from each other enormously. The rejected claims are not limited to the nucleic acids encoding reporters exhibiting high similarity to only those reporters which are well characterized (Note claims that are so limited such as claims 18, 71, 74, 76-78, 80, 83-85, and 96 are not rejected).

Applicants argue that the disclosures of WO 99/14336 and Arnold show that it is routine in the art to screen for multiple substitutions or multiple modifications. However, this is not persuasive because the numbers of modifications present in the proteins addressed in these disclosures is well within the scope of what the examiner deemed enabled but the instant claims include much more. A skilled artisan would be well aware that as the number of modifications increases the number of possible sequences **increases** exponentially while the number of active sequences **decreases** exponentially. Thus both the amount of experimentation necessary make and test all possibilities as well as the level of predictability changes quickly. Applicants argue in response to the undue experimentation to prepare

variant reporters and screen them for activity, the fact that the outcome of such a screening program may be unpredictable is precisely why a program is carried out and thus it is unreasonable to contend that a program to locate biomolecules with target biological or physical properties would not be carried out by the art because the results cannot be predicted in advance. However, it is noted that applicants are not claiming the screening methods they are claiming the results of the screening methods which their own argument admits are unpredictable. Furthermore, while programs for making and testing for biomolecules with target biological or physical properties are routinely done in the art the scope of modifications used is vastly smaller in scope than the instant claims would require as even the most advanced techniques available at the time of the invention (i.e., high throughput mutagenesis and screening techniques) would allow for finding a few active mutants within several hundred thousand or possibly up to about a million inactive mutants as is the case for the claims deemed enabled (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within several billion or more as in the claims rejected would not be possible.

Claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 60, 67, 69, 70, 81, 86 and 90-95 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sherf et al. (US Patent 5,670,356) in view of Zolotukhin et al. (US Patent 5,874,304), Donnelly et al. (WO 97/47358), Pan et al., Cornelissen et al. (US Patent 5,952,547), and Hey et al. (US Patent 6,169,232) and claims 18, 47, 71, 74, 76-78, 80, 82-85, 87, 88 and 96 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sherf et al. (US Patent 5,670,356) in view of Zolotukhin et al. (US Patent 5,874,304), Donnelly et al. (WO 97/47358), Pan et al., Cornelissen et al. (US Patent 5,952,547), and Hey et al. (US Patent 6,169,232) as applied to claims 1, 3-6, 9, 11, 12, 15, 20, 21, 24-39, 41-45, 60, 67, 69, 70, 81, 86 and 90-95 above, and further in of Wood et al. (WO 99/14336).

Applicants argue that the combination of references does not disclose or suggest Applicant's invention as each reference discloses a different wav to modify the coding sequence of a different gene to increase expression. This is not persuasive because each of these references is drawn to methods of increasing the expression of a gene in a desired host by altering the sequence of the nucleic acid but not the encoded protein in a variety of ways which will lead to increases in the production of desired protein. The cited references show that

the art was clearly aware that a combination of changes in codon preference and removal of sequences detrimental to transcription and/or translation in either the wild type gene or the codon optimized version can be used to accomplish this goal. While each of the cited references used a different combination of types of modifications, the art clearly teaches all of the claimed modifications encompassed in applicants claims (i.e., mammalian codon optimization, removal of transcription factor binding sequences, removal of splice sites, removal of potential promoters, and removal of polyadenylation sites) and clearly teaches combinations of them with one or more of the others.

Applicants argue that while there is a general teaching in the combination of cited documents to alter codons and/or remove certain undesired sequences in a selected sequence, none of the cited documents teaches or suggests that codon alterations may create transcription factor binding sites. However, this is not persuasive because while none of the references may explicitly teach that that codon alterations may create unwanted transcription factor binding sites, several of the references clearly teach that codon alteration may create undesirable sequences in general, and several of the reference make it clear that transcription factor binding sites are undesirable sequences. As such a skilled artisan would have understood that

codon alterations may create unwanted transcription factor binding sites.

Applicants argue that to arrive at applicant's invention, one of skill in the art in possession of the cited documents would need to choose to identity specifically transcription factor binding sites, promoter sequences, splice sites, and polyA sites, as sequences to be removed by codon replacement although the references also teach removal of internal palindromic sequences, restriction endonuclease sites, glycosylation sites, ATTTA sequences, RNA polymerase termination signals, TA and CG doublets, blocks of G or C residues, inverted repeats, and long runs of purines. However, this is not persuasive as applicants claims are not drawn to any combination in particular and do not exclude removal of other detrimental sequences in addition to those specifically recited in the claims and the art clearly teaches several combinations of these.

Applicants argue that none of the cited documents suggests that a polynucleotide that is modified by replacement of nonmammalian codons with mammalian codons be further modified by replacement with other, lower usage mammalian codons to reduce the number of introduced mammalian transcription factor binding sites. However, this is not persuasive because several of the

references clearly teach that it may be necessary to replace high usage codons with lower usage codons for the elimination of undesired sequences.

Applicants argue that none of the cited documents discloses or suggests the use of software to identify particular regulatory sites, such as mammalian transcription factor binding sequences, in a database of transcription factor binding sequences. However, this is not persuasive as most of applicants claims do not even mention the use of software to identify sites to be removed. Furthermore, even for those claims that do mention this, it is noted that the claims recite products not processes. Patentability of a product recited in product-by-process format is determined by the characteristics of the product itself not by the recited method. A nucleic acid in which the sites to be removed were identified by an undefined computer program would not differ in any respect from a nucleic acid in which the sites to be removed were identified by any other method.

Applicants argue that one of ordinary skill in the art in possession of the cited art would have no reasonable expectation that any particular set of changes would improve activity in a gene that is to be expressed in a highly evolutionarily distinct cell. This is not persuasive because the art clearly provide an

expectation that codon optimization and the elimination of a variety of types of sequences which are detrimental to transcription and/or translation will improve the expression of a gene in a heterologous host. While it is acknowledged that one cannot be certain that the modifications will not have unexpected consequences, applicants are reminded that obviousness does not require an absolute certainty of success but only a reasonable expectation thereof. Applicants argue that the examiners previous statements that 1) it is obvious on its face that anytime a gene sequence is altered that one necessarily creates new sequences which were not previously present and that merely by random chance some of these newly created sequences may be detrimental and it is even further obvious on its face that the more changes one makes, the higher the chances that such a detrimental sequence will be introduced and 2) the remaining art clearly would have motivated one of skill in the art to make more substantial changes in codon preference within the luciferase of Sherf et al. are contradictory and questions why would one make more changes when more changes would just increase the chances that a detrimental sequence would be introduced. However, this is not persuasive because the art clearly suggests that one will obtain greater increases in expression with higher levels of optimization.

While this clearly increases the chances that a detrimental sequence will be **introduced**, the art also teaches how to remedy this potential drawback by rechecking the optimized sequence to eliminate newly created undesired sequences. Therefore, this potential drawback would not have prevented a skilled artisan from making more substantial changes in codon preference within the luciferase of Sherf et al.

Finally applicants argue that while it is relatively straightforward to remove ATTTA sequences, splice sites, restriction enzyme sites, prokaryotic promoter sequences, poly(A) signals, RNA polymerase termination signals, inverted repeats, long runs of purines, TA and CG doublets, and blocks of G or C residues of more than about 4 residues, to remove a plurality of transcription factor binding sites, by replacing codons, the modifications are selected in context, i.e., with reference to how those modifications impact adjacent sequences. However, this is not persuasive because while removing transcription factor binding sites might require more than a single nucleotide change to accomplish and might be more difficult than removing other sites, there is no reason to believe that a skilled artisan could not select alterations to the sequence which would eliminate these sites as well.

For all the reasons above, the rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Prouty
Primary Examiner
Art Unit 1652